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Abrupt withdrawal of atenolol in patients with severe angina

Comparison with the effects of treatment

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SUMMARY The effects of abrupt withdrawal of atenolol, a long acting cardioselective beta blocker, were studied in 20 patients with severe stable angina pectoris admitted to hospital for coronary arteriography. During the 144 hour postwithdrawal period no serious coronary events occurred. Mean and maximal daily heart rates rose steadily for at least 120 hours. No important arrhythmias were noted on ambulatory electrocardiographic monitoring. Treadmill exercise testing at 120 hours showed little reduction in the times to angina, ST depression, and maximal exercise when compared with those recorded at 24 hours. This deterioration was small when contrasted with the improvements in these indices produced by atenolol treatment in a similar group of patients not admitted to hospital.

No change in catecholamine concentrations or acceleration of the heart rate response to exercise occurred after atenolol withdrawal, suggesting that rebound adrenergic stimulation or hypersensitivity was absent or insignificant. Catastrophic coronary events after beta blockade withdrawal (the beta blockade withdrawal syndrome) have occurred almost exclusively in patients taking propranolol, many of whom had unstable angina at the time of withdrawal. This study showed that in patients with stable angina, even when severe, the abrupt withdrawal of atenolol can be expected to result in only minor clinical consequences. The risk to any patient of so called rebound events after withdrawal of beta blockade seems to be related to both the clinical setting and the agent being used.

Beta adrenergic blocking agents are widely used in patients with ischaemic heart disease, both in the treatment of angina and for secondary prevention of myocardial infarction.[1,2] While patients with angina would be expected to experience some symptomatic deterioration on withdrawal of beta blockade a few have suffered dramatic or catastrophic coronary events after beta blockade withdrawal; hence a specific beta-blockade withdrawal syndrome has been reported.[3–5]

Between 1973 and 1976 about 33 such cases were reported, all related to propranolol. These included patients who developed acute coronary insufficiency, acute myocardial infarction, or sudden death up to three weeks after propranolol withdrawal.[6–8] Although numerous beta blocking agents have been introduced since then, very few additional cases of the withdrawal syndrome have been reported.[9]

Atenolol is a widely used, long acting, water soluble, cardioselective beta blocker which has not as yet been associated with a withdrawal syndrome. Although this may be due to a lack of reporting as a result of general acceptance of the syndrome, the relatively long period for which beta blockade persists after atenolol withdrawal may possibly protect against these so called rebound events.[10]

This study was designed to document the effects of abrupt atenolol withdrawal on angina severity and exercise tolerance in a high risk group of patients admitted to hospital (group 1). Evidence of increased sympathetic output, which has been seen after beta blockade withdrawal in some hypertensive patients,[11] was sought by recording daily changes in heart rate and catecholamine concentrations for 120 hours after atenolol withdrawal.

To determine whether the adverse effects of

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atenolol withdrawal were disproportionate to its therapeutic effect, and thus consistent with a true rebound phenomenon, the changes in exercise test indices which relate to the severity of myocardial ischaemia—that is, times to angina and ST segment depression and total exercise time—which followed atenolol withdrawal were compared with those produced by atenolol in a similar group of angina patients not admitted to hospital (group 2).

Of the various mechanisms proposed for the beta blockade withdrawal syndrome, rebound adrenergic hypersensitivity has received the greatest attention.[11-13] In a study of euthyroid and hyperthyroid subjects this phenomenon was seen at 4–7 days after atenolol withdrawal.[14] To examine its possible clinical significance in patients with angina the rate of acceleration of heart rate during exercise, which in part relates to sympathetic responsiveness, was measured five days after withdrawal and compared with that in patients in group 2.

Patients and methods

Twenty patients with chronic stable angina (group 1) were selected for the study, which was to be carried out during hospital admission for coronary arteriography with a view to surgery. They were aged 36–60 (mean age 50) years; 19 were male and one was female. All had been receiving beta blockade for at least three months, and despite treatment with their current regimen of atenolol 100 mg daily all complained of class III or IV (NYHA classification) angina. Hypertensive patients and patients with unstable angina were excluded. No additional antianginal medication other than sublingual glyceryl trinitrate had been taken during the two weeks before admission.

Patients were admitted on day 0, when they received atenolol 100 mg at 0900. No further dose was given until day 6, 144 hours later, before discharge. They were questioned daily regarding any change in their angina pattern. Coronary arteriography was performed on day 3.

AMBULATORY MONITORING

Continuous ambulatory electrocardiographic monitoring (lead CM5) was performed from day 1 to day 5—that is, from 24 to 120 hours after the last dose. Oxford Medilog 1 recorders were used with Reynolds Pathfinder analysis. Total, peak, and mean heart rates for each 24 hour period were calculated, together with the total number of extrasystoles and ST segment trends.

EXERCISE TESTING

Maximal treadmill exercise testing using a modified Bruce protocol and 12 lead electrocardiographic monitoring was performed at 24 and 120 hours after the last dose of atenolol. The electrocardiogram was recorded at rest and after each minute of exercise. Arm blood pressure was recorded at one minute intervals using a sphygmomanometer.

These two tests were performed so that changes in exercise performance and threshold for myocardial ischaemia resulting from atenolol withdrawal might be measured quantitatively. Without an initial exercise test before treatment with atenolol it would, however, be impossible to state with certainty whether a deterioration in exercise tolerance between days 1 and 5 represented a true rebound phenomenon or simply the removal of a beneficial effect. Since a pretreatment test was not performed, the exercise test results of these patients (group 1) were compared with those in a group of 28 patients with stable class II to IV angina who were being given atenolol 100 mg daily as their only treatment (group 2). Using the same exercise protocol, these patients were exercised before treatment and again after four weeks of treatment, the second test being at two hours after a morning dose. The changes in exercise performance in group 2 thus reflect the objective benefits of atenolol treatment and provide a valid yardstick with which to compare the deleterious effects of withdrawal. The Table shows the clinical features of the two groups.

HEART RATE CHANGES DURING EXERCISE

The rate of acceleration in heart rate was defined as the absolute change in heart rate during exercise (maximum rate minus resting rate) divided by the number of minutes exercised. This value in beats per minute was calculated for group 1 patients on day 5 and for group 2 patients before treatment.

Table *Clinical features of 20 patients in whom atenolol was withdrawn (group 1) and in 28 starting treatment with atenolol (group 2)*

	Sex (M/F)	*Age (yr)*		*Grade of angina*			
		Mean	*Range*	*I*	*II*	*III*	*IV*
Group 1	19/1	50	36–60	0	0	4	16
Group 2	24/4	52	32–61	0	7	6	15

CATECHOLAMINE EXCRETION

Plasma noradrenaline concentration was measured daily from day 1 to 5 in the first seven patients by the radioenzymatic method of Henry *et al*,[15] both after resting supine for 30 minutes and after tilting at 65° for five minutes.

Twenty four hour urinary excretion of catecholamines was measured in 11 patients by the trihydroxyindole method; the amines were extracted with alumina at pH 8·5 and the final fluorescence was read in a Perkin-Elmer spectrofluorimeter. The excretion of vanilmandelic acid in the urine was measured in these patients by the spectrophotometric method of Pisano *et al*.[16]

STATISTICAL ANALYSIS

All statistical analysis was by Students paired *t* test for within group comparisons and by the unpaired *t* test for comparisons between groups 1 and 2.

Results

SYMPTOMATIC CHANGES (GROUP 1)

No serious complication arose during the withdrawal period, and no patient required the early reintroduction of beta blockade. No patient complained of so called withdrawal symptoms such as palpitation, headache, or anxiety.[12] Three patients noticed a worsening of their angina, and one had a 30 minute episode of rest pain on day 5; all three experienced very easily induced angina on day 1—that is, by the fourth minute of the exercise protocol.

Coronary arteriography was performed without incident on day 3. Eighteen patients had multivessel disease and two had single vessel disease.

AMBULATORY MONITORING (GROUP 1)

Analysis of peak and mean heart rates for each 24 hour period was possible in 10 patients (Fig. 1) A steady day to day increase was seen, with no rebound tachycardia.

The number of ventricular extrastysoles tended to increase as beta blockade disappeared (from 255 (64) (mean (SD)) on day 2–3 to 492 (954) on day 5–6 ($p<0·05$)). No episodes of tachyarrhythmia were seen.

Analysis of ST segment changes was possible in nine patients. Two had more ST depression on day 5–6 than on day 2–3 but none showed a stepwise trend of worsening ST depression.

EXERCISE TESTING (GROUPS 1 AND 2)

Figure 2a shows the exercise times to angina and to 1 mm ST depression and the total duration of exercise on days 1 and 5 in group 1. In the group as a whole there was a small significant reduction in the time to

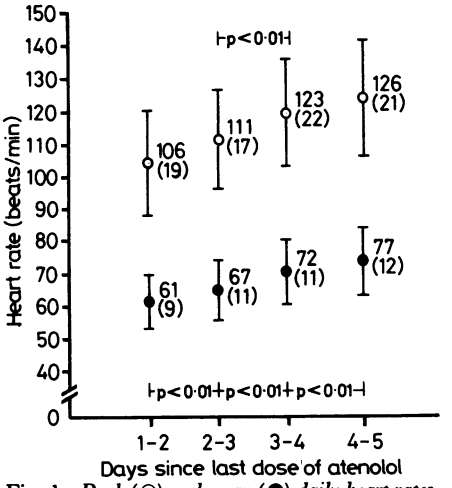

Fig. 1 *Peak (○) and mean (●) daily heart rates in 10 patients (group 1) after atenolol withdrawal recorded by continuous ambulatory electrocardiographic monitoring. Values are mean (SD).*

ST depression on day 5 but no change in the time to angina or the total exercise time. Individually, eight patients showed >10% deterioration in the exercise time to both angina and ST depression on day 5, but in no instance was this particularly pronounced. Seven patients showed no deterioration in either index, while two patients showed improvement in both.

Figure 2 also shows the results of exercise testing in the patients in group 2, performed before and during atenolol treatment. These twenty eight patients derived a highly significant benefit from atenolol, which in every respect exceeded the deterioration which followed atenolol withdrawal in the patients in group 1.

Heart rate changes

The mean resting heart rate in group 1 patients before exercise testing on day 5 was 79 (13) beats/min compared with 72 (13) beats/min in untreated group 2 patients (NS). During exercise testing heart rates rose by a mean of 8·8 (7·4) beats/min in group 1 and by 10·0 (5·3) beats/min in group 2 (NS). One patient in group 1 was exercised for only 1·3 minutes on day 5 compared with 3·0 minutes on day 1; on both occasions he had an exaggerated heart rate response to exercise (17 beats/min on day 1 and 35 beats/min on day 5). Angina developed within the first minute of both tests. This patient had very severe coronary disease with impaired left ventricular function and died during aortocoronary bypass surgery three weeks later. If he is excluded from the analysis then a significantly slower rate of rise in heart rate occurred

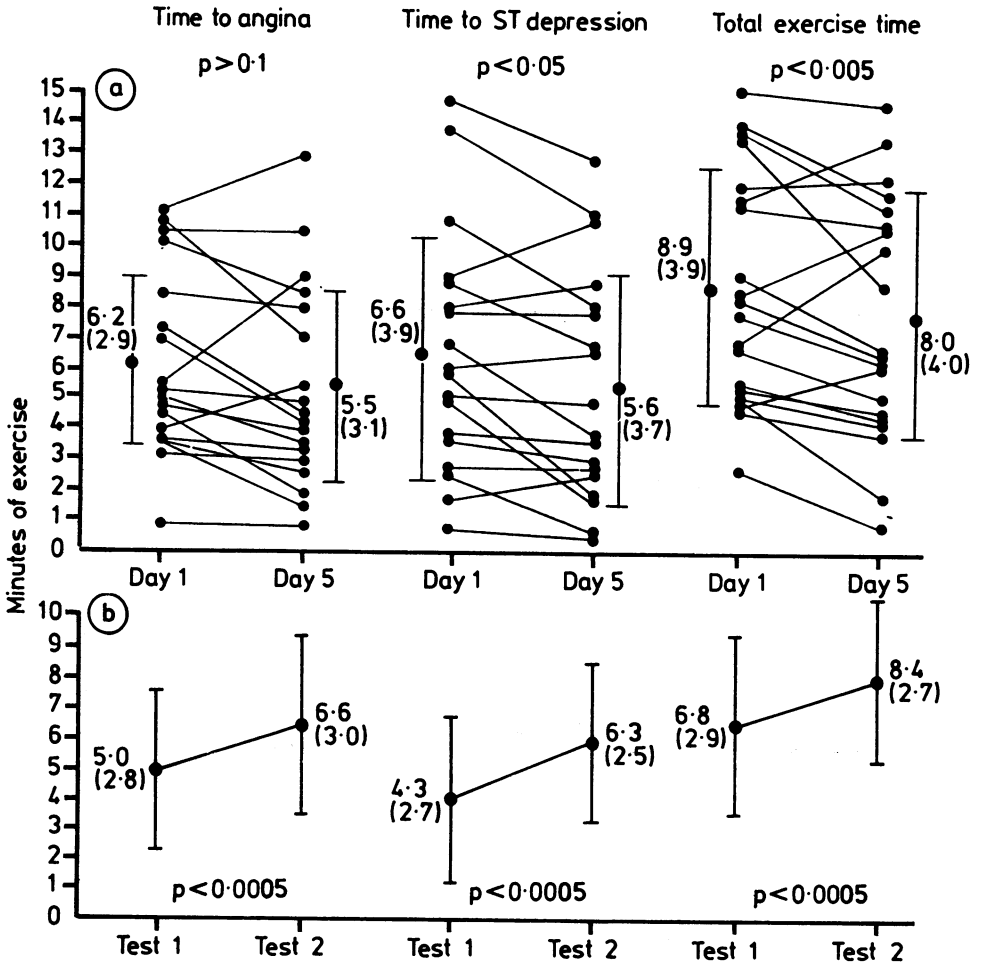

Fig. 2 *Results of treadmill exercise testing in (a) 20 patients (group 1) performed 24 hours (day 1) and 120 hours (day 5) after atenolol was last taken (individual values and mean (SD) values are shown; values for only those 18 patients who developed angina or ST depression on both days 1 and 5 are given) and (b) 28 patients (group 2) performed before (test 1) and during treatment with atenolol 100 mg daily (test 2). Test 2 took place after four weeks' treatment two hours after a morning dose. Values are mean (SD).*

after atenolol withdrawal than in the patients in group 2 (7·4 (4·3) *vs* 10·0 (5·3) beats/min, $p<0·05$).

CATECHOLAMINE EXCRETION

Figure 3 shows the plasma noradrenaline estimations. No trend of rising or falling concentrations was seen. Day to day variations during recumbency and tilting fell within the range of variability found in a small group of healthy, untreated subjects, whose noradrenaline concentrations were measured on two separate days (Fig. 4). Thus mean concentrations in seven patients in group 1 showed day to day variations of up to 35% (recumbent) and 6% (tilted), while individual variability of up to 73% and 25% respectively was observed in the healthy subjects. One patient showed a 100% increase in noradrenaline concentration during recumbency on the day of coronary arteriography, compared with the previous day's concentration but little further rise on tilting. On every other day his recumbent concentration was around 500 ng/l. This patient explains the high mean value on day 3.

Figure 5 shows the urinary catecholamine and vanilmandelic acid excretions. Again, no significant changes followed atenolol withdrawal.

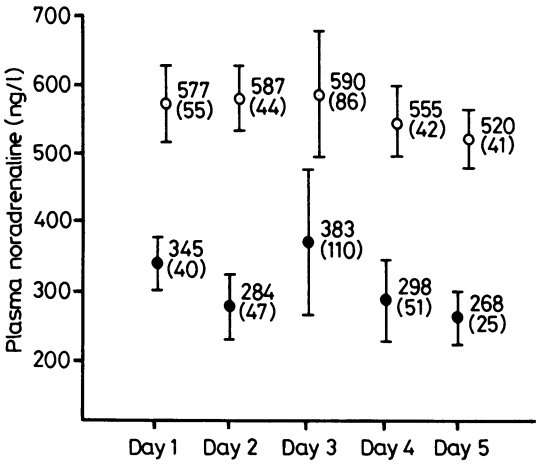

Fig. 3 *Plasma noradrenaline concentrations measured daily for five days after atenolol withdrawal in seven patients in group 1, supine (●) and after tilting (○) at 65° for five minutes. Values are mean (SEM).*

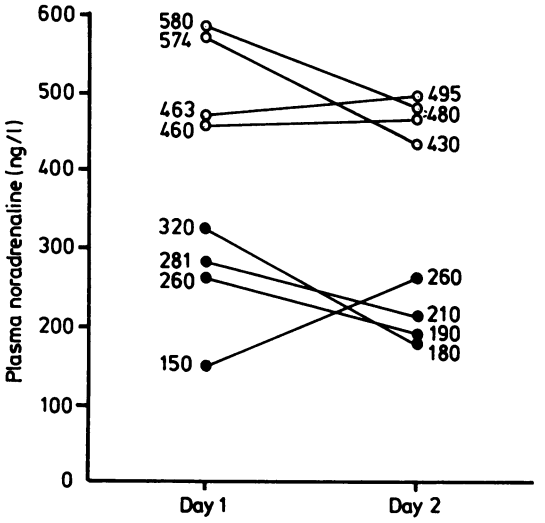

Fig. 4 *Plasma noradrenaline concentrations measured in four healthy, untreated subjects on two separate days supine (●) and after tilting (○) at 65° for five minutes.*

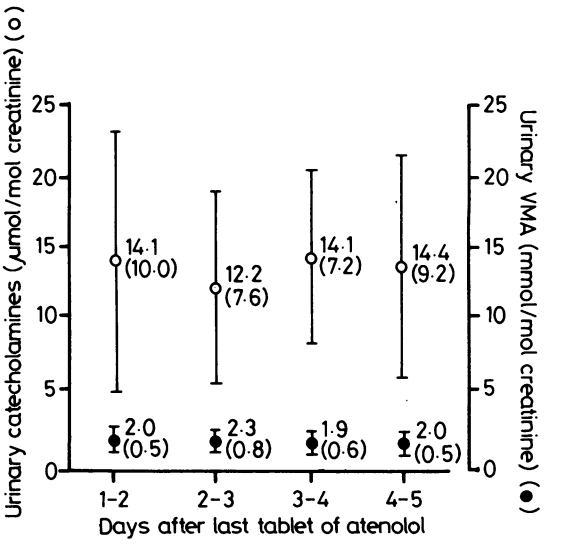

Fig. 5 *Twenty four hour urinary catecholamine (○) and vanilmandelic acid (VMA) (●) excretion measured daily in 11 patients for five days after atenolol withdrawal. Values are mean (SD).*

Discussion

Many of the case reports describing the beta blockade withdrawal syndrome concerned patients with worsening or unstable angina at the time of withdrawal.[4] This contrasts with planned studies of beta blockade withdrawal such as the present study, which have for ethical reasons excluded such patients. Thus in one prospective series in 100 consecutive patients admitted for coronary arteriography propranolol was withdrawn for a mean period of 39 hours.[17] Ninety patients reported no worsening of angina, and coronary events were no more frequent than in the period preceding withdrawal. In a retrospective study the morbidity among 55 inpatients in whom propranolol had been withdrawn for a mean of 80 hours was no greater than in 47 control patients who continued to take propranolol.[18] Since propanolol is of proven value in treating stable angina[19] the absence of any apparent symptomatic deterioration in such inpatients is presumably the result of the reduction in physical activity which follows admission to hospital. It could be argued that the postwithdrawal periods in these two studies were too short, since propranolol withdrawal phenomena appear to be most common between four and seven days after stopping treatment.[4 12] Our study endeavoured to assess symptomatic changes objectively using two standardised exercise tests; the first at a time when therapeutic beta blockade was present and the second during the period when rebound hypersensitivity and hence symptomatic deterioration should have been most pronounced.[12 14] We used a postwithdrawal period of 144 hours, which with hindsight could perhaps have been made even longer since at 96 hours after the last dose there was evidence of persisting beta blockade on ambulatory heart rate analysis.

Comparison of the two exercise tests showed a surprisingly small symptomatic deterioration after

atenolol withdrawal: of the times to angina and ST depression and the total exercise time, only the time to ST depression was significantly reduced. This was in sharp contrast to the improvement in each of these exercise test indices produced by atenolol treatment in the patients in group 2. This disparity was not due to an absence of effective beta blockade on day 1, since heart rates both before and at peak exercise were much lower on day 1 than on day 5 (61 (8) and 114 (19) beats/min respectively on day 1 *vs* 79 (13) and 131 (19) on day 5, $p<0.01$); neither was the symptomatic status of the two groups of patients very dissimilar, as judged by their exercise test performances without atenolol (compare Figs. 2 and 3). More probably, the apparent discrepancy between the effects of treatment and withdrawal resulted from the difference in the timing of exercise tests in the two groups (24 hours after atenolol in group 1 and two hours after atenolol in group 2),[20] together with a small training effect and some possible persistence of beta blockade on day 5. In the event, it seems reasonable to conclude that atenolol withdrawal led to a lowering of the exercise threshold for myocardial ischaemia which was certainly no greater than the removal of its therapeutic effect and which therefore was not in keeping with a rebound phenomenon.

It has been suggested that withdrawal phenomena might be prevented by a gradual tailing off of the dose of beta blocker.[4 8 21] This study and others[22-24] show that even after withdrawal of shorter acting agents such as propranolol there is a gradual increase in heart rate over several days, suggesting that a gradual reduction in dosage is unnecessary.

The mechanisms by which beta blockade withdrawal might cause catastrophic coronary events remain controversial. The chief action of these agents in angina is to reduce myocardial oxygen demand, mainly by reducing heart rate and double product.[24-26] It has reasonably been suggested that by causing a rise in these determinants of oxygen consumption beta blockade withdrawal could cause myocardial ischaemia and necrosis even under resting conditions.[3 4 8] In the present study, however, myocardial ischaemia, as shown by angina and ST segment depression, developed at considerably higher heart rates (up to 35 beats/min) and double products on day 5 than on day 1. This effect of atenolol (and other beta blockers[27]) of reducing considerably the heart rate at which angina develops was even more pronounced in the group 2 patients (97 (15) beats/min during treatment *vs* 120 (15) beats/min before treatment, $p<0.0001$). Therefore, while beta blockade withdrawal increases the basal heart rate, the rate at which ischaemia develops is reset at a higher level; hence, in some patients atenolol withdrawal produced no deterioration, just as in some patients beta blockade produces no objective benefit.[28-30]

A second mechanism proposed for withdrawal phenomena is rebound hypersensitivity of cardiac beta receptors to circulating catecholamines.[11-13] While hypersensitivity to infused isoprenaline has been seen after propranolol withdrawal in hypertensive[12] and normal[11] subjects other studies have not confirmed this phenomenon.[31 32] At the time when rebound hypersensitivity is said to be present after atenolol withdrawal[14] no acceleration of the heart rate response with exercise was seen in our patients in group 1 when compared with group 2. In the one patient who had an exaggerated response the cause was almost certainly exercise induced pump failure[33] since it was present on day 1 as well as on day 5. An exaggerated heart rate response to exercise was observed in five normal subjects at 66 hours after propranolol withdrawal, but not when these subjects were withdrawn from atenolol.[34] Thus although adrenergic hypersensitivity may occur after atenolol withdrawal by mechanisms which increase sympathetic drive,[14] it appears to exert no influence on the heart rate response during normal physical activity.

An increase in the concentrations of circulating catecholamines after beta blockade withdrawal has been found in some hypertensive patients[12] while in others the concentrations fell[35] or did not change.[36] In a normotensive group of patients with angina (a group resembling our own) Lindenfeld *et al* found no change in plasma noradrenaline concentration after propranolol withdrawal[32]; similarly, in a small group of normal normotensive subjects no change in plasma noradrenaline concentrations followed withdrawal of either propranolol or atenolol.[34] Alterations in concentrations of circulating catecholamines after beta blockade withdrawal may therefore be peculiar to hypertensive subjects, in whom abnormal sympathetic activity has been reported.[37]

Thus the abrupt withdrawal of atenolol in 20 patients with severe angina produced minor clinical effects which were no greater than those expected from the removal of its therapeutic effect and was unaccompanied by evidence of sympathetic overactivity or adrenergic hypersensitivity. Serious coronary events after beta blockade withdrawal have occurred almost exclusively in patients with severe or worsening angina who were taking shorter acting agents, and in such patients the abrupt stopping of treatment outside hospital would obviously be unwise. While rare idiosyncratic reactions to beta blockade may have occurred, and could never be ruled out by a prospective study, this study shows that the clinical consequences of abrupt atenolol withdrawal are usually minor and predictable corresponding with a gradual disappearance of beta blockade over several days. In patients with less severe or no angina atenolol with-

drawal would therefore be expected to carry no appreciable risk of precipitating a coronary event.

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